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INNATE CYTOKINES DICTATE THE FATE OF ACUTE INTESTINAL INFLAMMATION

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The interleukin 1 (IL-1) family consists of eleven proteins, which are further organized into 3 subfamilies. IL-1 α and IL-1 β , which belong to the IL-1 subfamily, have been long recognized as integral components of innate immune processes. As such they are implicated in the pathogenesis of several inflammatory diseases, including Inflammatory Bowel Disease (IBD). Moreover, therapeutic neutralization of IL-1 β and now also of IL-1 α are integrated into clinical practice. Bersudsky et al. aimed to dissect the specific roles of IL-1 α and IL-1 β during acute colitis and restitution, following injury by administration of dextran sulfate sodium (DSS) in mice (*Bersudsky, M, Luski, L, Fishman, D et al. Gut* 2014; 63:598). The two cytokines exerted opposite roles, as indicated by the differential natural course of acute DSS-colitis in mice deficient for IL-1 α or IL-1 β . IL-1 α KO mice demonstrated attenuated colitis with no mortality and significantly less weight loss, fecal bleeding and histological damage. Furthermore, epithelial restitution was intact, with intense epithelial cell proliferation, preservation of barrier function and abundant expression of the tight junction protein, claudin-3. In sharp contrast, mice deficient for IL-1 β had severe colitis as well as lethality. Significant histological damage was still present 7 days post-DSS cessation, indicating failure of healing mechanisms, such as defective epithelial proliferation, increased epithelial permeability and absent claudin-3 signal by immunohistochemistry. These findings clearly point to a pro-inflammatory role of IL-1 α and a protective role of IL-1 β during acute inflammation/repair of the gut mucosa. Accordingly, neutralization of IL-1 α via an anti-mouse IL-1 α -specific monoclonal antibody led to decreased severity of DSS-colitis in wild-type mice, whereas administration of the IL-1-receptor antagonist (IL-1Ra), which blocks both IL-1 α and IL-1 β , had no ameliorating effect on colitis.

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Bersudsky et al. elegantly showed that this diverse function is paralleled by differential cellular sources of the two cytokines. In wild-type mice with acute DSS colitis, IL-1 α localized to epithelial cells. The severity of DSS-colitis did not differ between IL-1 α KO mice and mice carrying a deletion in the *il-1a* gene specifically in intestinal epithelial cells, emphasizing the functional importance of epithelial-derived IL-1 α . Conversely, the main cellular source of IL-1 β was infiltrating lamina propria monocytes, which was inflammation-specific, as IL-1 β immunostaining was not seen in noninflamed mice. The protective role of monocyte-derived IL-1 β was further confirmed by the demonstration of attenuated DSS-colitis in bone marrow chimeras of irradiated IL-1 α - or IL-1 β -deficient mice that were reconstituted with wild-type hematopoietic cells. In fact, IL-1 β -deficient mice that received hematopoietic cells capable of producing IL-1 β demonstrated normal repair mechanisms after acute injury. Moreover, Bersudsky et al. also found that the milder form of colitis in IL-1 α -deficient mice was associated with increased numbers of CD8+ and CD4+ cells with a regulatory immunophenotype (CD3+CD4+CD25+FOXP3+). This implies a role for “innate” cytokine IL-1 α in the shaping of adaptive immune responses after acute mucosal injury.

Commentary

The paradigms for the pathogenesis of IBD have been reappraised in recent years. Traditionally, over-reactive adaptive immune responses were considered as the sole critical mediators of chronic mucosal inflammation. Today, acute inflammatory events have emerged as similarly important, as they may lead to breakdown of homeostasis and initiation of chronic immunological activation. In healthy individuals, acute inflammation disrupts homeostasis only transiently and is followed by complete functional and anatomical healing initiated by growth factors within the pro-inflammatory cytokine milieu. In contrast, under the pressure of disease-associated genetic polymorphisms, patients with IBD may fail to upregulate such restorative factors, leading to unrelenting activation of pro-inflammatory pathways, and defective restoration of mucosal integrity.

Bersudsky et al. shed new light into the multifaceted role of “innate” cytokines in gut homeostasis by exploring the role of IL-1 α and IL-1 β during acute inflammation and repair. Following DSS administration, both cytokines are increased at the injured mucosa. Nevertheless, despite the fact that they use the same receptor and have the same signal, their effects are quite opposite in this experimental setting. The specific function largely depends on the cellular source and pattern of expression of each cytokine. Upon DSS-inflicted injury, necrotic epithelial cells release IL-1 α and acting as an “alarmin”, contribute to active inflammation by recruiting neutrophils that further harm barrier integrity. However, this type of acute inflammation is self-limiting, as inflammatory monocytes are subsequently attracted, which release growth factors that lead to tissue repair. This healing process is dependent upon monocyte-derived IL-1 β , secreted several days post-injury. IL-1 α - and IL-1 β -deficient mice do not develop IBD spontaneously, yet when DSS disrupts the epithelial barrier, inflammation develops. Thus, similar to human IBD, a triggering event may be necessary for the functional consequences of certain genetic defects to be revealed.

The IL-1 α precursor is constitutively present in healthy intestinal epithelial cells but upon cell death or injury it is released, acting as a strong pro-inflammatory factor, which triggers the initial inflammatory injury. This is due to the “alarmin” like property of the IL-1 α precursor (*Frontiers Immunol.* 2013 Nov 20;4: 391). It is somewhat of a paradox that the potent potentially pro-inflammatory IL-1 α is present in intestinal epithelial cells of mice and humans without inflammation. Under such homeostatic conditions, the IL-1 α precursor shuttles back and forth between the nucleus and the cytosol, as long as there is no necrotic epithelial cell death. When there is apoptotic cell death of intestinal epithelium, IL-1 α is tightly bound to nuclear DNA and not available for binding to the IL-1R1. By contrast, when epithelial cells undergo necrosis, as is induced by DSS, intracellular IL-1 α precursor is released to the environment, promoting inflammation in two ways: first, by acting as an “alarmin” and second, by generating pro-inflammatory mature IL-1 α , after cleavage by local proteases (*Mol Cell* 2011;44: 265). The alarmin function may explain why this cytokine propagates acute DSS colitis, in contrast to other epithelial “innate” factors, which ameliorate the severity of disease by preserving homeostatic mechanisms (*Gastroenterology* 2011; 140: 1729).

IL-1 β , on the other hand, is produced by lamina propria monocytes and facilitates tissue repair. This beneficial effect stands in contrast to the pro-inflammatory role that has been traditionally attributed to IL-1 β . Nevertheless, it has been reported that peripheral monocytes from patients with Crohn’s disease with mutations of the NOD2 or NLRP3 genes failed to upregulate IL-1 β upon stimulation with muramyl dipeptide, or LPS, respectively (*Lancet* 2005; 365:1794; *Nature Genetics* 2009; 41: 71). In light of the current findings, hypoproduction of IL-1 β may be detrimental to gut homeostasis after transient injury and promote chronic inflammation. In all, it can be said that inflammation consists of both harmful and beneficial components and patients with IBD bearing such polymorphisms are deprived from the latter. Mice deficient in IL-1 β also demonstrated diminished expansion of CD8 $^{+}$ and CD3 $^{+}$ CD4 $^{+}$ CD25 $^{+}$ FOXP3 $^{+}$ cells. This raises the possibility IL-1 β may promote the generation of regulatory lymphocyte populations. This would be in contrast with models of chronic intestinal inflammation, where IL-1 β was also shown to promote the expansion of TH17 effector lymphocytes (*J Exp Med* 2012; 209: 1595). A defective mechanism to control expansion of IL-1 β may take place in patients with polymorphisms in the autophagy ATG16L1 gene (*Nature* 2008; 456: 264). Autophagy is fundamentally protective and reduces inflammation by preventing the processing and secretion of IL-1 β . Thus defective autophagy results in more secretion of IL-1 β and worsening inflammation.

To date three IL-1 blockers have been approved for clinical applications (*Seminars in Immunology* 2013; 25: 469). Given the diverse roles of IL-1 α and IL-1 β during intestinal inflammation, the potential application of these agents for the treatment of IBD should take into account these differences. The IL-1Ra, anakinra, blocks the IL-1 receptor, which is common for IL-1 α and IL-1 β , thus preventing both the pro-inflammatory effect of IL-1 α and the protective effect of IL-1 β . This may explain why in the study by Bersudsky et al. administration of anakinra had no effect, and why IL-1R KO mice did not display a specific phenotype after DSS administration (*J Exp Med* 2010; 207:1625). Canakinumab, a monoclonal antibody neutralizes only IL-1 β without affecting IL-1 α . Rilonacept, a soluble decoy receptor targets both IL-1 β and IL-1 α . Given the protective role for IL-1 β in the

mouse models, blocking IL-1 β would be detrimental. In contrast, the use of a human anti-human-IL-1 α monoclonal antibody may benefit patients with IBD, as the administration of anti-IL-1 α (MABp1) resulted in reduced inflammation, reversal of lean body mass loss, improved quality of life and prolonged survival in patients with end stage cancer cachexia (*Lancet Oncol.* 2014; 15: 656).